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(54) USE OF ACETYL-D-AMINOGLYCOSAMINE IN TREATMENT OF LOCAL LESIONS AND SYSTEMATIC SYMPTOMS RELATED TO INFECTIONS OF VIRUS OR BACTERIA

(57) The present invention discloses a use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating local lesions or systematic symptoms caused by infections of virus or bacteria. A parenteral preparation comprising N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof as active component is capable of controlling systematic toxic symptoms caused by infections of virus and bacteria and local and systematic lesions caused by endotoxins and exotoxins, and exhibits an excellence rate of 90%.

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Description

Technical field

[0001] The present invention relates to the use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the treatment of local lesions and/or systematic symptoms caused by infections of virus and/or bacteria, and the use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of local lesions and/or systematic symptoms caused by infections of virus and/or bacteria.

Background Art

[0002] The systematic toxic symptoms caused by infections of virus and/or bacteria include systematic toxic symptoms caused by endotoxemia and local ectotoxic lesions, such as fever, headache, vertigo, delirium, nausea, emesis, general malaise, etc. At present, there are two main methods for treatment of systematic symptoms caused by infections of bacteria: 1) antibacterial therapy, and 2) supporting therapy.

[0003] Viral infections are commonly caused but not limited by Coxsackie virus, ECHO virus, orthomyxovirus, paramyxovirus, adenovirus, coronaviruses, reovirus, respiratory syncytial virus, rhinovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, and encephalitis B virus, which result in systematic symptoms such as fever, etc. accompanying by local mucosal lesions. The most usual symptoms are inflammations, including tracheitis, bronchitis, mucous hyperemia, and exhibit cough and asthma. At present, there is no means or drug to effectively control viral infections, except for some supporting therapies.

[0004] In the research of "bio-wave" theory, the present inventor has set up a organism wave-growth model. Through deeply researching the molecular mechanism of the organism wave-growth, the inventor puts forward a micro-heterology variation mechanism, wherein the biological wave of organism continuously changes; the change rate depends on the change extent of outer environments; after the organism is infected by bacteria and viruses, the environments in the organism changes quickly, which promotes the generation of micro-heterology and the non-equilibrium between the organism and environments, and causes local lesions and systematic toxic symptoms. According to molecular biological analysis, these lesions and toxic symptoms relate to the instability even loss of function of proteins, especially various enzymes under changed conditions, especially changed temperature in the presence of microorganism metabolism products. The systematic toxic symptoms mainly appear in nerve system, including headache, delirium, hypersomnia, coma, general malaise, muscular soreness, nausea, emesis, blurred vision, diplopia, respiration disorder (first tachypnea then bradypnea), arrhythmia, urinary and fecal incontinence, even torpidity or loss of reflex, local congestion, edema, blood clot and tissue necrosis.

[0005] It is found that N-acetyl-D-glucosamine as a regulating factor of biological wave affects not only the macro fluctuation, but also the stability of vibration of bio-macromolecular substances. This substance can maintain the physiological vibration of bio-macromolecular substances, alleviate and repulse harmful effects in organism, in order to maintain the physiological function of macromolecular substances. In general, said substance can control symptoms, alleviate lesions, promote heal, and eliminate toxic effects.

[0006] The inventor surprisingly finds that N-acetyl-D-glucosamine or pharmaceutically acceptable salts in combination with various pharmaceutically acceptable carriers can form a liquid dose form for treatment of local lesions or systematic toxic symptoms caused by infections of virus or bacteria.

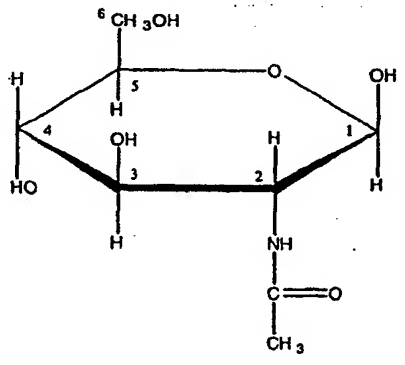
Contents of the invention

[0007] One object of the present invention is to provide a use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the treatment and control of local lesions and systematic symptoms caused by infections of virus or bacteria.

[0008] Another object of the present invention is to provide a use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment and control of local lesions and systematic symptoms caused by infections of virus or bacteria.

[0009] Another object of the present invention is to provide a method for treating local lesions and systematic symptoms caused by infections of virus or bacteria.

[0010] The N-acetyl-D-glucosamine used in the present invention is a compound having a molecular formula of $C_8H_{15}NO_6$ and a structure formula (I).



[0011] The examples of pharmaceutical acceptable salts of N-acetyl-D-glucosamine that can be used in the present invention include, but are not limited to: the salts formed with inorganic acids, such as hydrochloride, hy-

drobromide, borate, phosphate, sulfate, hydrosulfate and hydrophosphate, and the salts formed with organic acids, such as citrate, benzoate, ascorbate, methylsulfate, picrate, fumarate, maleate, malonate, succinate, tartrate, mesylate, and glucose-1-phosphate.

[0012] In a pharmaceutical composition of the present invention, the content of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof is generally 0.1-10% by weight.

[0013] Besides N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof, said pharmaceutical composition further comprises excipients or carriers well known in the art to form a preparation suitable for intravenous injection, subcutaneous injection, intramuscular injection, intraperitoneal injection, etc.

[0014] Said pharmaceutical composition can be administered in a manner of single dose per day or multi-doses per day, such as 3-4 doses per day. The dose of said pharmaceutical composition depends on patient's age, condition, symptom, and administration manner. In general, as to an adult patient having a bodyweight of 75 kg, the dose of said pharmaceutical composition is 1-100000 mg per day, preferably 100-10000 mg per day based on active component, and is administered one to four times daily.

[0015] According to a preferable model, N-acetyl-D-glucosamine is administered in a manner of intervenous drop infusion during the therapeutical procedure in order to potentiate power of resistance, to replenish water, and to maintain stability in vivo.

[0016] As compared to conventional supporting therapy, N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof are more effective in reducing local inflammations and alleviating local lesions and systematic toxic symptoms, act quickly and roundly, and facilitate better prognostic results.

[0017] Although the inventor does not intend to be restricted by any theory, it is believed that N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof can stabilize important molecules of organism and maintain the physiological function of bio-macromolecules, thereby avoiding some complications after infections of virus or bacteria and expediting the healing. Thus, N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof are desired drug for supporting therapy.

Embodiments for carrying out the invention

[0018] The present invention and beneficial effects thereof are further demonstrated by the following examples, but it shall be understood that these examples are merely to illustrate the present invention, rather than to restrict the scope of the present invention in any aspect.

Example 1. *Promoting wave test of the compound of formula (I)*

1. Experimental materials and method:

1.1 Sample: pure compound of formula (I)

1.2 Experimental materials:

[0019]

Strain: *Proteus Mirabilis* that meets the following biochemical reaction characteristics: dynamics (+), urease (+), lactose (-), glucose (+), H_2S (-),phenylalanine deaminase (+).

Culture medium: modified LB culture medium (components: 1% tryptones, 0.5% yeast extract, 1% sodium chloride, 0.1 % glucose, 0.002% TTC, and pH = 7.2 to 7.4).

1.3 Experimental method:

[0020]

Control sample: the *Proteus Mirabilis* were inoculated at the center of LB plate, incubating at 37°C for 9 hours;

Test sample: the compound of formula (I) with a final concentration of 0.5% was added to the LB plate, then the *Proteus Mirabilis* were inoculated by the same method, and cultured at 37°C for 9 hours.

2. Experimental results and evaluation:

[0021] The control sample exhibited concentric rings with an interval of 3 hours, which extended outward continually. The test sample showed not only concentric rings with an interval of 3 hours, but also many fine waves on each ring in comparison with the control sample.

[0022] The experiment adopts a bio-wave model to research the promoting wave function of the compound of formula (I). The results showed that the compound of formula (I) was not only able to cause bacterial cell to reveal a normal bio-wave characteristic, but also cause the wave reveal finer wave mode. These indicated that the compound of formula (I) has a function of promoting bio-waves. This wave-promoting function may explain the effects of using N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof for treating and controlling local lesions and systematic symptoms caused by infections of virus or bacteria.

Example 2. *Toxicological test of the compound of formula (I)*

[0023] The toxicological test of the compound of formula (I) includes:

1. Acute toxicity test: including tests of oral administration, intravenous injection administration, and maximum limit amount for administration;

2. Ames test;

3. Micronucleus test of mouse bone marrow cell;

4. Abnormality test of mouse sperm;

5. Aberration test of mouse testis chromosome;

6. Chronic lethal test;

7. Sub-chronic toxicity (feed for 90 days) test;

8. Traditional deformity-inducing test.

[0024] The results of these tests showed that in the acute toxicity test of the compound of formula (I), the acute toxicosis reaction had not appeared when the dosage more than 2 g/kg was taken; in the long-period toxicity test, the maximum dosage had reached up to 1 g/kg, and after the treatment and observation for four weeks, there was no intoxication reaction yet; and in the reproduction test, the mice were feed with a routine dosage of 7 mg/kg for 3 generations, it had been proved that the compound of formula (I) had no influence on the pregnancy, birth, nurse and the growth of baby mouse, so that the compound of formula (I) is a substance without toxicity.

Example 3. *Cytological tests of regulating micro-heterology variation*

[0025] Conventional incomplete 1640 culture media were used for cell culture, and B16 tumor cells (commercially obtained from the tumor cell library of Shanghai Institute of Cytobiology) were inoculated on said media. After being continuously cultured for more than 48 hours, the micro-heterology variation of cells and the control effects of N-acetyl-D-glucosamine thereon were observed under a condition where metabolic wastes affected the growth environment. After N-acetyl-D-glucosamine having a final concentration of 1 g/100ml was added to the culture media, the cell number stably increased with the culture time during the cell growth procedure. The control cells cultured without N-acetyl-D-glucosamine could not proliferate on the same culture media under same conditions. These tests indicated that in the presence of the compound of formula (1), cells could regulate the cell micro-heterology variation in order to adapt to the ever-changing environment, so that cells could proliferate continuously.

Example 4. *Animal tests that N-acetyl-D-glucosamine regulates micro-heterology variation*

[0026] B16 tumor cells were inoculated on superior parts of hind legs of 50 rats, and 5% aqueous solution of the compound of formula (1) was intraperitoneally injected to the rats for consecutive 7 days, 3 times per day, and 1 ml every time. Finally, solid tumor did not appear in 45 rats. In control group without the administration of the compound of formula (1), many proliferative corpuscles appeared in at least 40 among 50 rats within 1-3 days after the tumor cells were inoculated; many immature cells appeared within 3-5 days; and visible solid tumors finally appeared within about 10 days. As compared to the control group, this did not appear in the test group, which indicated that the compound of formula (1) could control the micro-heterology variation.

Example 5. *Animal tests of controlling local lesions and systemic symptoms caused by infection of microorganism*

[0027] 10 rabbits were used in tests. The rabbits were administered with a culture of Gram-negative bacteria (Pseudomonas aeruginosa, serotype 8, wherein the bacterial number in the culture is about 3×10^{11}) in a dose of 10 ml per day for consecutive 3 days. The rabbits exhibited serious toxic symptoms, such as fever, increased heart rate, tachypnea, hyperposia, bodyweight drop, and after 5 days, the rabbits exhibited watery stool, increased nasal secretion, systematic emaciation and exhaustion. The rabbits were intravenously administered with N-acetyl-D-glucosamine (10% aqueous solution) a dose of 2 ml every time, 3 times per day, for consecutive 3 days. The rabbits were gradually healed after one week, they began to eat, their symptoms were alleviated, their body temperatures dropped, and their defecation formed. After examination of nasal mucosa and respiratory tract of the rabbits, the inflammations were alleviated, and their secretion products were normal. In the test group, all 10 rabbits survived, while in the control group, 8/10 rabbits of the control group died within one week, and only 2 rabbits survived.

[0028] When N-acetyl-D-glucosamine was replaced with N-acetyl-D-glucosamine hydrochloride in the tests (other conditions were not changed), 7/10 rabbits of test group survived. The test group was significantly different from the control group.

Claims

1. A use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for controlling local lesions and sys-

tematic symptoms caused by infections of virus or bacteria.

2. A use according to claim 1, wherein said medicament is a preparation suitable for intravenous injection, subcutaneous injection, intramuscular injection, or intra-peritoneal administration.

3. A use according to 1 or 2, wherein the dose of said medicament for an adult patient is 1-100000 mg per day based on the active component, and said medicament is administered 1-4 times daily.

4. A method for controlling local lesions and systematic symptoms caused by infections of virus or bacteria, wherein a pharmaceutical composition comprising an effective amount of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof is administered to a patient.

5. A method according to claim 4, wherein said pharmaceutical composition is a preparation suitable for intravenous injection, subcutaneous injection, intramuscular injection, or intra-peritoneal administration.

6. A method according to 4 or 5, wherein the dose of said pharmaceutical composition for an adult patient is 1-100000 mg per day based on the active component.

7. A use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in controlling local lesions and systematic symptoms caused by infections of virus or bacteria.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2004/000281

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K31/7008, A61P31/00, 39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chinese Medical Abstracts, CNKI

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, WPI, PAJ, CA, MEDLINE, CNKI, glucosamine,acetyl, 氨基葡萄糖,葡萄糖胺, 乙酰

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US4772591, 20. Sept. 1988, See entire document	1-3
A	EP0372730, 13. Jun. 1990, See entire document	1-3
A	WO90/08549, 9. Aug. 1990, See entire document	1-3
A	US5217962, 8. Jun. 1993, See entire document	1-3
A	CN1372931A, 9. Oct. 2002, See entire document	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" carlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24, Jun. 2004(23.06.2004)	
Name and mailing address of the ISA/ 6 Xitucheng Rd., Jimen Bridge, Haidian District, 100088 Beijing, China Facsimile No. 86-10-62019451	Authorized officer Jiang Hui Telephone No. 86-10-62085236

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2004/000281

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4-7
because they relate to subject matter not required to be searched by this Authority, namely:
claims 4-7 are directed to methods of treatment of the human/animal body.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant,this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant.Consequently ,this international search report is restricted to the invention first mentioned in the claims;it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA /210 (continuation of first sheet (2)) (January 2004)

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